Medical and Pediatric Oncology 29:544–552 (1997)

Hodgkin Disease in Children: Results of a Prospective Randomized Trial in a Single Institution in Argentina

Federico Sackmann-Muriel, MD,* Pedro Zubizarreta, MD, Guillermo Gallo, MD, Marcelo Scopinaro, MD, Daniel Alderete, MD, Elizabeth Alfaro, MD, Sandra Casak, MD, Guillermo Chantada, MD, María Sara Felice, MD, and Rubén Quinteros, MD

Purpose. To compare prospective treatment strategies in childhood Hodgkin disease to the following subsets of patients: a) Favorable prognostic group: these patients were randomized to receive 6 vs. 3 CVPP chemotherapy cycles without radiotherapy (CVPP: cyclophosphamide, vinblastine, procarbazine, and prednisone. The scheme was repeated every 28 days). b) Intermediate prognostic group: these patients were randomized to receive 6 cycles of CVPP or AOPE (AOPE: Adriamycin, vincristine, prednisone, and etoposide). Between the third and fourth cycles, all patients in this group received radiotherapy (RT)(30–40 Gy to initially involved areas). c) Unfavorable prognostic group: those patients received a single arm regimen of 6 cycles of CCOPP/CAPTe (3 of each combination) every 28 days. All these patients received radiotherapy (30–40 Gy to initially involved areas).

Results. From October 1987 to December 1994, a total of 114 children and adolescents were evaluated. Mean age was 9 (range 2–17) years. There were 72 boys and 42 girls. With a median follow-up of 5 (range 1.5–8.7) years, at 80 months event-free survival (EFS) and overall survival (OS) for the whole cohort are 0.809 (SE: 0.04) and 0.873 (SE: 0.04), respectively (SE: Standard Error). Favorable prognostic group (n = 26) EFS is 0.831 (0.09) (Arm CVPP × 3: 0.857 (0.13) and Arm CVPP × 6: 0.875 (0.08); p = non significant). Intermediate prognostic group (n = 64) EFS is 0.806 (0.05) (Arm CVPP × 6 + RT: 0.872 (0.05) and Arm AOPE × 6 + RT: 0.667 (0.10); p = 0.04). Unfavorable group (n = 24) EFS is 0.829 (0.07).

Conclusions. Results of treatment for the whole group are satisfactory. However, 3 cycles of CVPP without radiotherapy obtain equal EFS than 6 cycles without radiotherapy in the favorable prognostic group. In the intermediate prognostic group, 6 cycles of CVPP plus radiotherapy obtain a superior EFS than 6 cycles of AOPE plus radiotherapy. With the success of treatment for Hodgkin disease in children, future research needs to be focused in reducing toxicity without altering the excellent actual outcome. Med. Pediatr. Oncol. 29:544–552, 1997. © 1997 Wiley-Liss, Inc.

Key words: Hodgkin disease in children; Hodgkin disease: treatment without radiotherapy; Hodgkin disease: treatment; Hodgkin disease: treatment according to prognostic index

INTRODUCTION

Over the last 30 years, the prognosis of Hodgkin disease has improved impressively with the use of combination chemotherapy with or without radiotherapy. Hodgkin disease is the childhood malignancy with current highest cure rate. Five-year survival in children and adolescents is approximately 90% [1–5]. Thus, since it seems almost impossible to increase survival substantially, major efforts have been made to reduce late sequel induced by treatment (i.e. potential organ damage and second malignancies). Epidemiological studies have demonstrated clear geographic variations in underdeveloped countries when compared with developed ones [6,7]. The purpose of this study is to report 114 children with Hodgkin disease diagnosed and treated in a single institution in Buenos Aires, Argentina. They were clinically staged and stratified into three risk groups according to Argentine Group for Treatment of Acute Leukemia's (GATLA) prognostic index for Hodgkin disease: favorable, intermediate and unfavorable [8]. Each prognostic group received a specially designed therapeutic approach. Moreover, patients of the favorable and intermediate groups were prospectively randomized in two different regimen arms.

Hematology/Oncology and Pathology Departments, Hospital de Pediatría ''Prof. Dr. Juan P. Garrahan,'' Buenos Aires, Argentina.

*Correspondence to: Federico Sackmann-Muriel, M.D., Head Hemato/Oncology Department, Hospital de Pediatría ''Prof. Dr. Juan P. Garrahan,'' Combate de los Pozos 1881, (1245) Buenos Aires, Argentina. E-mail: garrahan @ giga.com.ar

Received 26 September 1996; Accepted 29 April 1997

MATERIALS AND METHODS

From October 1987 to December 1994, 117 previously untreated consecutive children and adolescents with Hodgkin disease were prospectively registered in this study at the Hospital de Pediatría ''Dr. Juan P. Garrahan.'' Our series is forming part of a wider national study which included adults and children. Randomizations, stratified by institution, permitted us to analyze our pediatric results separately. Our institution is an open pediatric Hospital that attends children from all economic levels in Argentina. However, near half of the patient population belongs to a low income group without health insurance. This study was approved by our institutional clinical trial review committee.

The diagnosis was established by a lymph node biopsy and interpreted by the guidelines established by Lukes and Butler in 1966 [9] and reviewed by one of us, (G.G.) for this presentation. At the time of diagnosis, pretreatment clinical staging included a detailed patient history with special reference to the presence of symptoms ''B'' (fever, sweat, and/or weight loss), complete blood count, Westergren method of erythrocyte sedimentation rate, renal and liver function test, chest X-ray, abdominal ultrasound, computed tomographic scan of the chest, abdomen, and pelvis. Liver biopsy and bilateral crest bone marrow biopsies were required for advanced stages. Bipedal lymphography was recommended but not mandatory, it was performed only in a few children during the first months of the present study. As world wide accepted, this procedure was rapidly replaced by CT scanning. Our children were not explored with both methods at the same time, so that a comparison is precluded. No child underwent laparotomy with staging splenectomy. Staging was performed under joint discussion according to the Ann Arbor criteria [10,11] clarified by Cotswolds' meeting statements [12]. ''Bulky'' mediastinal disease was defined as a mass greater than one-third of the thoracic diameter at the level of the fifth thoracic vertebrae.

Patients were prospectively allocated according to a previously described prognostic index (based on four parameters: age, symptoms, stage, and of involved nodal regions) in three groups: favorable, intermediate, and unfavorable [8].

Score to define the prognostic index:

Age (years)	Symptoms (*)	Stage	Number of involved regions
≤15 = 0	A = 0	I = 0	<3 = 0
16–30 = 1	B1 = 1	II = 1	3–4 = 1
31–45 = 2	B2 = 2	III = 2	5–6 = 2
>45 = 3	B3 = 3	IV = 3	>6 = 3

(*)A: absence; B: presence (number of symptoms).
Staging according to prognostic index:
Favorable Group: Score 0–3 (if ''bulky'' mediastine, upgrade to intermediate group).
Intermediate Group: Score 4–5.
Unfavorable Group: Score > 5.

Studies of long-term treatment related morbidity were not performed prospectively. However, the report of the pulmonary, cardiac, and endocrinologic studies will be the subject of a separate publication.

Treatment Plan

Favorable and intermediate prognostic patients received treatment according to stratified and randomized subsets. The *favorable prognostic group* was randomized between arm A and B. *arm a*: Six monthly cycles of cyclophosphamide 600 mg/m^2 days 1 and 8, vinblastine 6 mg/m^2 days 1 and 8, procarbazine 100 mg/m^2 PO days 1–14, and prednisone 40 mg/m^2 PO days 1–14 (CVPP). *arm b* received only 3 monthly cycles of the same chemotherapy regimen (CVPP). On April 1992, an interim evaluation demonstrated no statistical differences on event-free survival between both arms, subsequently all favorable group patients were allocated on Arm B. Radiotherapy was not delivered to these patients if they achieved CR. The *intermediate prognostic group* was randomized between arm C and D. *arm c:* consisted of three CVPP cycles, radiotherapy to the areas initially involved in a 30–40 Gy schedule (30 Gy if in complete remission after the third cycle or 40 Gy if not in remission after the mentioned cycle), followed by another 3 cycles of CVPP. *arm d*: consisted of three monthly cycles of adriamycin 45 mg/m^2 IV on day 1, vincristine 1.5 mg/m^2 IV on day 1 (max. dose 2 mg), prednisone 100 mg/m^2 PO on days 1–5, and etoposide 150 mg/m^2 IV on days 1 and 3 (AOPE), radiotherapy to the areas initially involved (30 Gy if in complete remission after the third cycle or 40 Gy if not in remission after the mentioned cycle), followed by another 3 cycles of AOPE. On April 1992, an interim evaluation demonstrated significant differences in favor of Arm C. Thus, Arm D was closed and all intermediate group were subsequently allocated to Arm C. The *unfavorable prognostic group* received 6 cycles, every 28 days, or two more after achieving complete remission. In this subset, two chemotherapy combinations were employed in an alternating scheme: a) CCOPP: CCNU 100 mg/m^2 PO on day 1, Vincristine 1.4 mg/m^2 IV on days 1 and 8 (no maximal dose), procarbazine 100 mg/m^2 PO on days 1–14, and prednisone 40 mg/m^2 PO on days 1–14. b) CAPTe: Cyclophosphamide 600 mg/m^2 IV on day 1, adriamycin 50 mg/m^2 on day 1, prednisone 40 mg/m^2 PO on days 1–5, and Teniposide 100 mg/m^2 IV on day 1. All patients received a consolidation with radiotherapy on initially involved areas: 30 Gy if in complete remission after the fourth cycle (2 CCOPP/2 CAPTe) or 40 Gy if not in remission after the mentioned cycle.

Evaluation of Response

A remission evaluation was performed at completion of therapy in all patients. Another evaluation took place

in the intermediate group after the third cycle and in the unfavorable group after the fourth to define radiotherapy dosage. Complete remission was defined as the clinical and/or radiological disappearance of at least 70% of all tumor masses. Partial remission was defined as a reduction of 50% or more during a period of more than 4 weeks. Failure was defined as either a less than 50% shrinkage of the mass or early recurrence before radiotherapy was started.

Statistical Methods

Event-free survival (EFS) and overall survival (OS) was estimated by Kaplan Meier analysis [13]. EFS was measured from the time of remission to relapse, death or true last visit. For patients not achieving complete remission with the first treatment, EFS time is 0. The associated standard error (SE) was calculated by the method of Peto et al. [14]. Difference in survival curves were assessed by the log-rank test [15]. Response rate, death on induction and relapse rate were evaluated for statistical significance by the x^2 analysis. Data was updated to June 15th, 1996.

RESULTS

Of the total 117 patients registered in this study, 3 were not evaluable for the following reasons: the parents refused the proposed treatment in one case and one patient was lost to follow-up 1 month after diagnosis. A third patient was a protocol violation: she was a girl who belonged to the intermediate prognostic group and was insufficiently treated with the favorable risk regime with 3 courses of CVPP and relapsed 2 months later. She attained a second remission after more chemotherapy (CVPP/AVBD). With a survival of +24 she was lost to follow-up. We did not have any more data from any of them. Thus, a total of 114 patients are evaluable.

Patient characteristics are listed in Table I. Mean age at diagnosis was 9 (range: 2–17) years. Twenty three (20.2%) patients were ≤5 years and 2 children were 2 years of age. There were 72 boys and 42 girls, male/female ratio: 1.71. All children were Hispanic.

The correlation of clinical staging and prognostic group is depicted in Table II.

At the completion of treatment (chemotherapy only, in favorable prognostic group and chemo-radiotherapy, in intermediate and unfavorable prognostic groups) 107 (93.9%) patients had achieved complete remission (CR), 1 (0.9%) patient achieved partial remission, 3 (2.6%) patients failed and 3 (2.6%) patients died on induction. Results according to prognostic groups and treatment arm are depicted in Table III. There are no statistically significant differences in therapy results among the prognostic groups. Responses to treatment varied according to clinical stages: 94% of IA and IIA patients achieved CR, while only 71% of patients with Stage IV did (Table IV).

TABLE I. Characteristics of 114 Patients

Age: Mean: 9 years.
Range: 2–17 years.
Sex: Male: 72 patients.
Female: 42 patients.
M/F ratio: 1.71.

Stage	n	%
IA	32	28.07
IB	4	3.50
IIA	21	18.42
IIB	11	3.65
IIIA	17	14.91
IIIB	22	19.30
IVA	2	1.75
IVB	5	4.38
Histology	**n**	**%**
Nodular sclerosis	43	37.72
Mixed Cellularity	59	51.75
Lymphocyte predominance	11	9.65
Lymphocyte depletion	1	0.88
Prognostic Group	**n**	**%**
Favorable	26	22.8
Intermediate	64	56.1
Unfavorable	24	21.1

TABLE II. Comparison of Clinical Staging vs. Prognostic Group in 114 Patients

Clinical staging	n		n	Prognostic group
IA	32		17	
IIA	21		4	
n = 53			1	Favorable
			2	n = 26
			2	
IB	4			
IIB	11			
n = 15			15	
			17	
			3	
IIIA	17		9	Intermediate
IIIB	22		15	
n = 39			3	n = 64
			2	
IVA	2			
IVB	5		19	Unfavorable
n = 7			5	n = 24

Actuarial EFS and OS for the whole cohort are shown in Figure 1. Median follow-up was 5 (range: 1.5–8.7) years by June 1996. At 80 months, the EFS (SE) was 0.809 (0.04) and the OS (SE) was 0.873 (0.04). Actuarial EFS (SE) according to clinical stage is 0.87 (0.07) for stage I, 0.737 (0.08) for stage II, 0.842 (0.05) for stage III, and 0.714 (0.17) for stage IV (Figure 2). EFS (SE) according to prognostic group is shown in Figure 3. In the favorable prognostic group the EFS is 0.831 (0.09),

TABLE III. Response According to Prognostic Group and Treatment Arm

Group	n	CR (%)	PR	Failure	Death
Favorable					
Arm A	10	10 (100)	–	–	–
Arm B	16	15 (94)	1	–	–
Intermediate					
Arm C	43	42 (98)	–	–	1
Arm D	21	18 (86)	–	3	
			–	–	–
Unfavorable	24	22 (92)	–	–	2
Total	114	107 (94)	1	3	3

TABLE IV. Response to Treatment According to Clinical Stage

Stage	n	CR (%)	PR	Failure	Death
IA–IIA	53	50 (94)	1	1	1
IB–IIB	15	15 (100)	–	–	–
III	39	37 (95)	–	1	1
IV	7	5 (71)	–	1	1
Totals	114	107 (94)	1	3	3

for the intermediate prognostic group, 0.806 (0.05), and for the unfavorable group, 0.829 (0.07) (p = n.s.). At 80 months, EFS estimates for each randomization arm were as follows: Arm A: 0.857 (0.13) and Arm B: 0.875 (0.08) in the favorable prognostic group (p = n.s.); Arm C: 0.872 (0.05) and Arm D: 0.667 (0.10) in the intermediate prognostic group (p = 0.04).

Treatment Failures

There were 19 treatment failures, either on induction (n = 7) or after attaining CR (n = 12). As mentioned previously, a remission evaluation was performed at the completion of treatment. One stage I patient of the favorable prognostic group achieved a partial remission after 3 CVPP courses. He was treated then with the ABVD regimen (6 courses) and achieved CR. He is disease-free +29 months after diagnosis. Three patients (stage I: 1, stage III: 1, and stage IV: 1) of the intermediate prognostic group were treated with AOPE arm and developed progressive disease. They were then treated with the unfavorable prognostic treatment strategy (CCOPP/CAPTe) and all achieved CR and they are disease-free +32, +35, and +73 months from diagnosis. All partial remission and progressive disease cases are considered for outcome evaluation as EFS: 0.

Two patients died on induction. Two (stage IIA and IIIB, 1 intermediate and 1 unfavorable prognostic group, respectively) died of septic cause in neutropenia after 5 and 2 courses of chemotherapy, 6 and 2 months after diagnosis. Another one, stage IV, died of refractory progressive disease 18 months after diagnosis.

After achieving CR, 12 patients failed. One patient died in CR of complications derived from an associated congenital disease: Duchenne muscular dystrophy (65 months after diagnosis). One patient developed a second malignancy. At 14 months from initial diagnosis, she developed a secondary acute myeloid leukemia FAB M5, Hodgkin disease-free, and died a few days later of overwhelming disseminated intravascular coagulation [16].

Ten patients relapsed, 7 boys and 3 girls: 8 belonged to the intermediate prognostic group with 4 patients in each treatment arm; in the favorable and unfavorable groups: 1 patient relapsed in each subset. The mean interval between the date of achievement of complete remission and the date of relapse was 12.7 (range: 5–26) months. There were two cases of cervical relapse after 30 and 40 Gy of local radiotherapy, respectively. Seven cases were originally of the nodular sclerosis histological subtype. Therapy was tailored for each patient. Four patients did not respond to salvage therapy and died of progressive disease. Complete remission was achieved in 6 patients, one of them subsequently relapsed and died of progressive disease. So 50% of patients obtained a second lasting complete remission and are presently alive. More details are given in Table V.

Toxicity

In relation to acute toxicity, both CVPP and AOPE combinations were usually well tolerated. Almost all children experienced nausea and vomiting with chemotherapy administration (particularly CVPP), though severe gastrointestinal toxicity was uncommon. None developed hemorrhagic cystitis. Leukopenia and neutropenia occurred in one third of patients and thrombocytopenia was mild. However, the CCOPP/CAPTe regimen was more myelotoxic and several times chemotherapy courses had to be delayed. Hematopoietic growth factors were not used in any case. All children were treated as outpatients.

Studies on long-term sequel were not performed prospectively. However, several patients have had studies of thyroid and pulmonary function. They will be the subject of a separate report.

DISCUSSION

The five-year survival for children and adolescents with Hodgkin disease is approximately 90% nowadays [1–5]. We had previously demonstrated that survival in childhood Hodgkin disease experienced a rather marked improvement during the last decades in Argentina [17]. A review of therapy results in 254 children <16 years of age with histologically proven Hodgkin disease and registered in three consecutive studies undertaken by the GATLA from November 1972 to December 1985 are published elsewhere [18].

In the present study, we report, at 80 months, an EFS

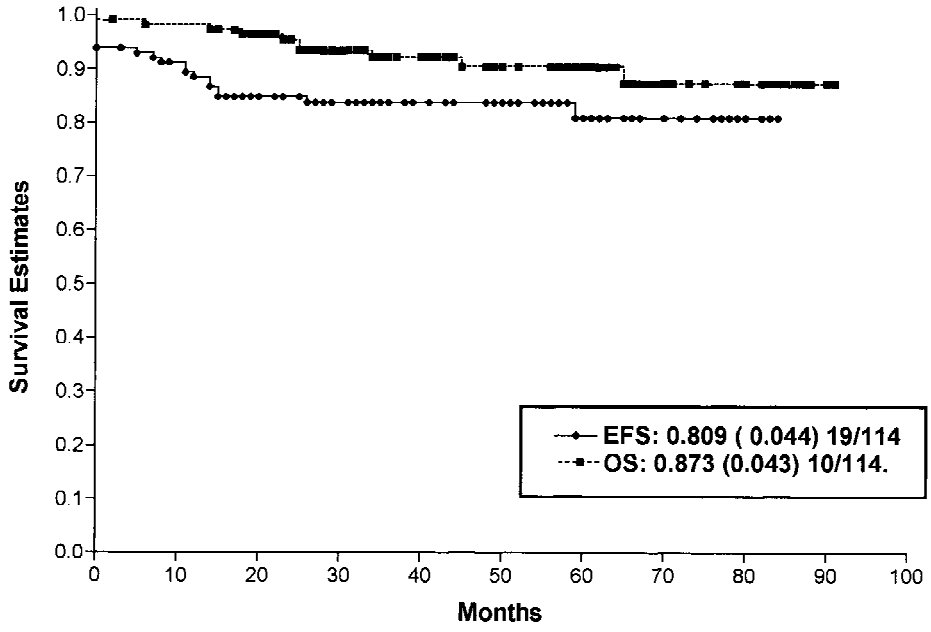

Fig. 1. Hodgkin disease Event-free and Overall Survival estimates at 80 months (Standard Error), n = 114 (events or deaths/total number of patients).

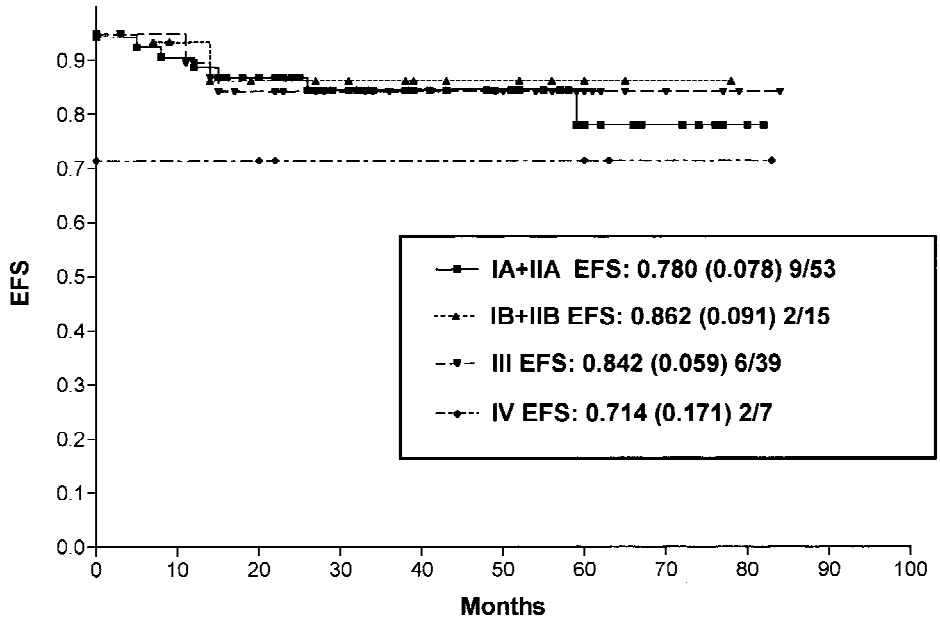

Fig. 2. Hodgkin disease Event-free Survival at 80 months (Standard Error) according clinical stage, n = 114 (events/total number of patients).

of 0.809 and an OS of 0.873 for an unselected population of children and adolescents consecutively diagnosed and treated in a single public children's hospital in Buenos Aires, Argentina. These results appear to be satisfactory. We have been careful to count non-responsive or progressive disease on therapy as an adverse event even for children successfully treated with an alternative regimen. We must recognize that the design of this study was conceived some 10 years ago, and perhaps some subsets of patients might have been overtreated. In the light of present data and our own results, we consider that the intensity of treatment for this disease might be decreased with no adverse impact in outcome.

The optimal treatment for childhood Hodgkin disease should warrant a high cure rate and low toxic effects especially in regard to long-term sequel. Radiotherapy, which had been advocated for many years as the main treatment modality for Hodgkin disease, bears pres-

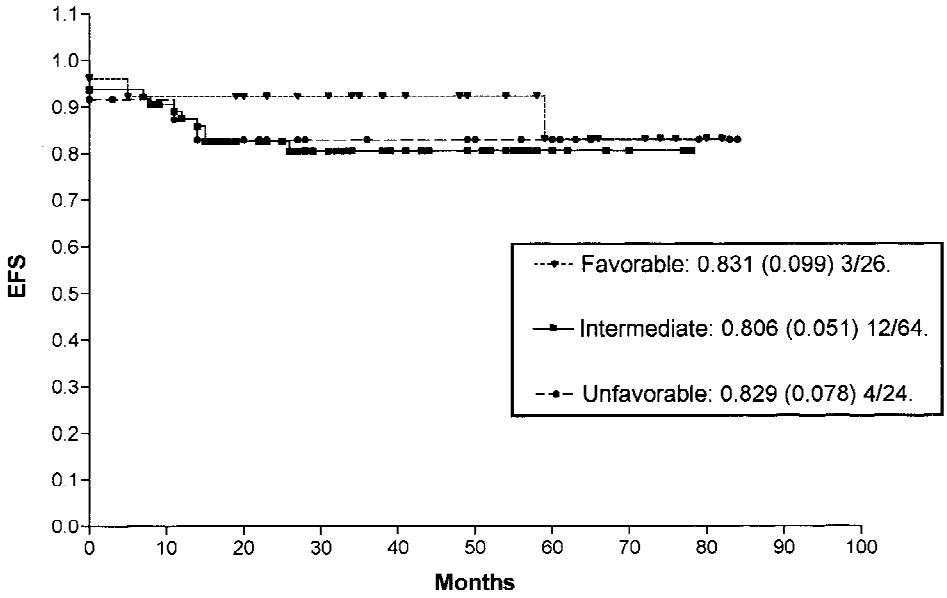

Fig. 3. Hodgkin disease Event-free Survival at 80 months (Standard Error) according to treatment prognostic group, n = 114 (events/total number of patients).

ently the burden of several long-term adverse effects. These include altered growth of irradiated tissues, asymmetric development, endocrine insufficiency, second solid malignancies, and early onset of cardiac vasosclerosis after mediastinal radiotherapy [19–24]. Chemotherapy may cause several late effects as well: anthracyclines may provoke cardiomyopathy, alkylating agents may cause male infertility and bleomycin may affect pulmonary function. Combined modality treatment leads to an increased risk in developing secondary leukemia [23,25].

In the present study we treated early stages of Hodgkin disease with chemotherapy and without radiotherapy. This design was based on a previous randomized study on clinical stages IA-IIA with 6 courses of CVPP vs. 6 courses of CVPP + plus involved field radiotherapy (30 Gy). In that study, 92 patients, children, and young adults, were evaluated. Forty-six on each arm. There were 6 relapses on the chemotherapy arm and 5 relapses on the chemo-radiotherapy arm [26]. Therefore, we decided to treat the favorable prognostic group with chemotherapy only: 6 vs. 3 courses of CVPP. Results show that 2 out of 16 patients and 1 out of 10 patients relapsed on each arm, respectively. Though the number of patients is small, EFS estimates were not statistically different. This suggests that early stages of Hodgkin disease in children can be treated with less than 6 courses of CVPP. Only a few studies are available to support the use of chemotherapy on it's own [24,27–34]. There have been no reported children series treated with chemotherapy alone in the United States. However, Maity et al. reported a carefully selected subset of 12 children treated at the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania with chemotherapy alone as initial therapy. Although the follow-up was short, ranging from 1.9–7.2 (median 4) years, these children did extremely well and had a 5-year EFS of 92% and an OS of 91% with only one failure [1]. This data is consistent with results achieved in the present study. We recognize that the number of patients in the favorable group is small. We have already mentioned that, in fact, our series is forming part of a wider national study which included adults and children and whose preliminary results were published by Pavlovsky et al. [34]. Randomizations, stratified by institution, permitted us to analyze our pediatric results separately. Pavlovsky reports on 78 patients allocated in the favorable group (Arm A = 36, Arm B = 42). The patients in their report are only those that entered *before* stopping the randomizations in 1992. They obtained non-significant differences between arms A and B then, and this finding persisted the same with a long follow-up.

In the intermediate prognostic group, it is interesting to find that the AOPE regimen, which avoids alkylating agents, is inferior to the CVPP combination, both arms receiving the same radiotherapy. Pavlovsky et al reports on 171 patients of the intermediate group (Arm C = 90, Arm D = 81). The patients in their report are only those that entered *before* stopping the randomization in 1992. They found significant differences between arms C and D then ($p = 0.015$), and this finding persisted the same with a long follow-up.

In the unfavorable prognostic group we administered a single arm treatment. The EFS estimate for this subset of patients is similar to the other risk groups keeping the level of 0.83.

TABLE V. Clinical Data and Follow-up of 10 Children Who Relapsed After Achieving Complete Remission

Patient	1	2	3	4	5	5	7	8	9	10
At diagnosis										
Age (years)	10	7	6	3	15	4	13	12	17	4
Sex	M	F	M	M	M	M	F	M	M	F
Histology	MC	NS	NS	LP	NS	NS	NS	NS	NS	MC
Stage	IIIA	IIA	IIA	IIA	IIIA	IIB	IIA	IIA	IIB	IIIB
Prognostic group	I	F	I	I	I	I	I	I	I	U
Treatment arm	D	B	D	D	D	C	C	C	C	–
Outcome										
EFS (months)	15	5	15	12	11	7	26	8	14	14
Site of relapse	Axilla (R), Preauricular	Cervical (L)	Spleen, retroperitoneal, Cervical (R)	Cervical + Supraclavic. (Billateral).	Spleen, Mediastinum	Cervical + Supraclavicular (L)	Peritoneal, Spleen	Epitroclear, Retroperitoneal.	Retrocrural, Cervical, supraclavicular.	Abdomen Spleen, Liver
Therapy for relapse	RT: Preauricular: 30 Gy. Axillar: 40 Gy	Cervical RT: 30 GY.	CCOPP/CAPTe × 6 + RT 25 Gy (Spleen, lumboaortic)	CVPP × 4	CCOPP/CPE × 5 (CPE: CAPE without DOXO)	CCOPP/CAPTe × 4 + RT: 40 Gy.	ABVD × 2 CVPP × 5	ABVD × 6 + RT: 26 Gy.	ABVD × 4 DECAL × 2	CCOPP/CAPE × 3 + RT: 40 Gy
Outcome/ Subsequent relapse	Complete Remission	Complete Remission	Complete Remission	2nd Local Relapse (DECAL × 1)	Non Remission	Complete Remission	Non Remission	Complete Remission	Non Remission	Non Remission
Survival	+44	+86	+67	25	25	+65	45	+41	23	34
Alive	Y	Y	Y	N	N	Y	N	Y	N	N

Histology: MC: Mixed Cellularity, NS: Nodular Sclerosis, LP: Lymphocyte Depletion. Prognostic Groups: F: Favorable, I: Intermediate, U: Unfavorable. Therapy for Relapse: CVPP, CCOPP, CAPTe: see text for schedule. ABVD: Adriamycin, Bleomycin, Vinblastine, and DTIC, DECAL: Dexamethasone, Etoposide, Cisplatin, Ara-c, and L-Asparaginase. RT: Radiotherapy.

It is worthy to remember that the prognostic index employed in this study was based on a multivariate analysis of 945 previously untreated clinically staged patients belonging to all ages, stages, histologies, and social status. All patients received combined chemotherapy with involved field radiotherapy. When the prognostic index was compared to the Ann Arbor classification using the Cox model, the former was selected with $p < 0.001$ vs. $p = 0.01$ for EFS and $p < 0.0001$ vs. $p = 0.11$ for OS [8]. It is interesting to find that all prognostic subsets of patients share the same survival estimates when they are treated appropriately for each stratified risk group. This confirms again the accuracy of our prognostic index, but as treatment regimens were not allocated according to Ann Arbor staging system, comparison with other series from the literature is precluded.

It is evident that radiotherapy doses of 30–40 Gy are too high and that they may yield unacceptable rates of second malignancies in the future.

Recently, Faría et al published a small series of patients from Brazil treated for Hodgkin disease with an OS estimate of 0.78 [35]. They mentioned that these results were lower than developed countries data [2,4,19], but similar to other underdeveloped countries [32,36–38]. Our results are more comparable to those of developed nations.

As mentioned above, we do not report long-term toxicity in this paper. Based on our previous report we know that thyroid dysfunction is present in 17% of patients after receiving 6 courses of CVPP and in 50% of those receiving 6 courses of CVPP plus mediastinal irradiation (30 Gy) [39]. So far, only one patient developed a second malignant disease (unfavorable prognostic group) with 3 courses of CCOPP and 3 of CAPTe plus 30 Gy of radiation on involved areas. She responded well but 14 months after her original diagnosis, being free of Hodgkin disease, she developed a secondary acute myeloid leukemia FAB M5. She died early, during the induction of remission therapy, of overwhelming disseminated intravascular coagulation [16]. We realize that more cases are expected to develop this devastating complication in our series because our follow-up is short and the risk to develop secondary leukemia is seen 3–9 years after first or subsequent treatment of Hodgkin disease [23].

At present we feel that early stages of Hodgkin disease in children should be treated primarily with combined chemotherapy. Radiotherapy should be reserved for patients not achieving complete remission with chemotherapy. Children with intermediate or advanced stages, a combined modality treatment should be given, consisting of moderate doses of radiotherapy (20 Gy) to involved areas, combined with chemotherapy such as ABVD or MOPP variants, preferably in an alternating or ''hybrid'' regimen. With this strategy, sequel of radiotherapy will be less severe than after 40 Gy extended field radiation, but nevertheless late effects are to be expected, though in a lesser degree.

REFERENCES

1. Maity A, Goldwein J, Lange B, D'Angio GJ: Comparison of high dose and low dose radiation with and without chemotherapy for children with Hodgkin's disease. An analysis of the experience at the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania. J Clin Oncol 10:929–935, 1992.
2. Oberlin O, Leverger G, Pacquement H, Raquin MA, Chompret A, Habrand JL, Terrier-Lacombe MJ, Bey P, Bertrand Y, Rubie H, Behar C, Zucker JM, Schaison G, Lemerle J: Low dose radiation therapy and reduced chemotherapy in childhood Hodgkin's disease: The experience of the French Society of Pediatric Oncology. J Clin Oncol 10:1602–1608, 1992.
3. Vecchi V, Pileri S, Burnelli R, Bontempi N, Comelli A, Testi AM, Carli M, Sotti G, Rosati D, Di Tullio MT, Grazia G, Massolo M, Aricó M, Collella R, Pession A, Rondelli R, Paolucci G: Treatment of Pediatric Hodgkin's disease tailored to stage, mediastinal mass, and age: An Italian (AIEOP) multicenter study of 215 patients. Cancer 72:2049–2057, 1993.
4. Schellong G, Hörning Y, Schwarze EW, Wannenmacher M: Risk factor adapted treatment of Hodgkin's lymphoma in childhood: Strategies and results of three consecutive multicenter studies in the Federal Republic of Germany. Recent Results in Cancer Research 117:205–213, 1989.
5. Weiner M, Leventhal BG, Marcus R, Brecher M, Ternberg J, Behm FG, Cantor A, Wharam M, Chauvenet A: Intensive chemotherapy and low dose radiotherapy for the treatment of advanced stage Hodgkin's disease in pediatric patients: A Pediatric Oncology Group Study. J Clin Oncol 9:1591–1598, 1991.
6. Correa P, O'Conor GT: Geographic Pathology of lymphoreticular tumors: summary of survey from geographic pathology. Committee of the International Union Against Cancer. J Natl Cancer Inst 50:1609–1617, 1973.
7. Hu E, Hufford S, Lukes R, Bernstein-Singer M, Sobel G, Gill P, Pinter-Brown L, Rarick M, Rosen P, Brynes R, Nathwani B, Feinstein D, Levine A: Third-world Hodgkin's disease at Los Angeles County, University of Southern California Medical Center. J Clin Oncol 6:1285–1292, 1988.
8. Pavlovsky S, Santarelli MT, Maschio M, for Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA). Definition of a valuable prognostic index in Hodgkin's disease based on a multivariate analysis in 945 patients. Proc of ASCO 7:240 (Abstract #928), 1988.
9. Lukes RJ, Butler JJ: The pathology and nomenclature of Hodgkin's disease Cancer Res 26:1063–1081, 1966.
10. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M: Report of the committee on Hodgkin's disease staging classification. Cancer Res 31:1860–1861, 1971.
11. Rosenberg SA, Boiron M, De Vita V, Johnson RE, Lee BJ, Ultmann JE, Viamonte M Jr.: Report of the committee on Hodgkin's disease staging procedures. Cancer Res 31:1862–1863, 1971.
12. Lister TA, Crowther D, Sutcliffe SB, Glastein E, Canellos GP, Young RC, Rosenberg SA, Coltman CA, Tubiana M: Report of a Committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds Meeting. J Clin Oncol 17:1630–1636, 1989.
13. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Amer Stat Assoc 53:457–481, 1958.
14. Peto R, Pike MC, Armitage P, Breslow EN, Cox DR, Howard SV, Mantel N, Mc Pherson J, Peto J, Smith PG: Design and analysis of randomized clinical trials requiring prolonged observation on

each patient. II Analysis and examples. Br J Cancer 35:1–39, 1977.
15. Tarone RE, Wara J: On distribution-free test for equality of survival distribution. Biometrika 64:156–160, 1977.
16. Felice M, Zubizarreta P, Chantada G, Alfaro E, Cygler AM, Gallego M, Sackmann Muriel F: Secondary acute myeloid leukemia (sAML) in children. Report of a single institution. Proc of ASCO 15:367 (Abstract #1085), 1996.
17. Sackmann Muriel F, Cebrian-Bonesana A, Pavlovsky S, Papendieck C, Morgenfeld M, Penchansky L, Schwartz L, Kvicala R, Sica M, Ojeda F: Hodgkin's disease in childhood. Therapy results in Argentina. Am J Pediatr Hematol Oncol 3:247–254, 1981.
18. Sackmann-Muriel F, Maschio M, Santarelli MT, Pavlovsky S: Results of therapy for Hodgkin's disease in childhood. The Argentine Group for Treatment of Acute Leukemia. In W.A. Kamps, G.B. Humphrey, S. Poppema (eds): ''Hodgkin's disease in children, controversies and current practice'' Boston, Kluwer Academic Publishers 1989, pp. 271–275.
19. Donaldson SS, Link MP: Combined modality treatment with low-dose radiation and MOPP chemotherapy for children with Hodgkin's disease. J Clin Oncol 5:742–749, 1987.
20. Donaldson SS, Kaplan HS: Complications of treatment of Hodgkin's disease in children. Cancer Treat Rep 66:977–989, 1982.
21. Robinson B, Kingston J, Noguira Costa R, Malpas JS, Barret A, Mc Elwain J: Chemotherapy and irradiation in childhood Hodgkin's disease. Arch Dis Child 59:1162–1167, 1984.
22. Boivin JF, Hutchison GB, Lubin JH, Mauch P: Coronary artery disease mortality in patients treated for Hodgkin's disease. Cancer 69:1241–1247, 1992.
23. Jenkin D, Greenberg M, Fitzgerald A: Second malignant tumors in childhood Hodgkin's disease. Med Pediatr Oncol 26:373–379, 1996.
24. Lange BJ, Meadows AT: Late effects of Hodgkin's disease treatment in children. In: W.A. Kamps, G.B. Humphrey, S. Poppema (eds) ''Hodgkin's disease in children. Controversies and Current Practice'', Boston, Kluwer Academic Publishers, 1989, pp. 195–220.
25. Meadows AT, Baum E, Fossati-Bellani F, Green D, Jenkin RDT, Marsden B, Nesbit M, Newton W, Oberlin O, Sallan SG, Siegel S, Strong LC, Voûte PA: Second malignant neoplasms in children: An update from the Late Effects Study Groups. J Clin Oncol 3:532–538, 1985.
26. Pavlovsky S, Dupont J, Jimenez E, Sackmann Muriel F, Montero C, Garay G: Randomized study of chemotherapy alone vs. chemotherapy plus radiotherapy in clinical stage IA-IIA Hodgkin's disease. In: F. Cavalli, G. Bonadona, and M. Rozencweig (eds), ''Malignant Lymphomas and Hodgkin's disease: Experimental and Therapeutic Advances''. Martinus Nijhoff Pub., Boston 1985, pp. 337–344.
27. Jacobs P, King HS, Karabus C, Hartley P, Werner D: Hodgkin's disease in children. A ten-year experience in South Africa. Cancer 53:210–213, 1984.
28. Ekert H, Waters KD: Results of treatment of 18 children with Hodgkin's disease with MOPP chemotherapy as the only treatment modality. Med Pediatr Oncol 11:322–326, 1983.
29. Ekert H, Waters K, Smith P, Toogood Y, Mauger D: Treatment with MOPP or CHIVPP chemotherapy only for all stages of childhood Hodgkin's disease. J Clin Oncol 6:1845–1850, 1988.
30. Ekert H, Fok L, Dalla-Pozza L, Waters K, Smith P, White L: A pilot study of EVAP/ABV chemotherapy in 25 newly diagnosed children with Hodgkin's disease. Br J Cancer 67:159–162, 1993.
31. Behrendt H, Brinkhuis M, Van Leeuwen EF: Treatment of childhood Hodgkin's disease with ABVD without radiotherapy. Med Pediatr Oncol 26:244–248, 1996.
32. Olweny CLM, Katongole-Mbidde E, Kiire C, Lwanga SK, Magrath I, Ziegler JL: Childhood Hodgkin's disease in Uganda: A ten-year experience. Cancer 42:787–792, 1978.
33. Sackmann-Muriel F, Lobo-Sanahuja F, Schvartzman E, Schwartz L, Dupont J: Treatment results in Hodgkin's disease in childhood: radiotherapy vs, chemotherapy alone. Proc Am Assoc Cancer Res 26:184, 1985.
34. Pavlovsky S, Schvartzman E, Magnasco H, Corrado C, Aris Cancela ME, Diez B, Cerutti I, Zirone S, Lastiri F, GATLA members: A randomized trial of CVPP for 3 vs 6 cycles in favorable prognosis and CVPP vs AOPE plus radiotherapy (RT) in intermediate prognosis for untreated Hodgkin's disease. Proceedings of ASCO 15:412 (Abstract #1259), 1996.
35. Faria SL, Vassallo J, Cosset JM, Brandalise SR: Childhood Hodgkin's Disease in Campinas, Brazil. Med Pediatr Oncol 26:90–94, 1996.
36. Dinshaw KA, Pande S, Advani S, Ramakrishnan G, Nair C, Tallvalkar G, Rao DN, Notani P, Rao R, Desai P: Pediatric Hodgkin's disease in India. J Clin Oncol 3:1605–1612, 1985.
37. Gad-El-Mawla N, El-Deeb BB, Abu-Gabal A, Abdel-Hadi S, Hamza MR, Zikri ZKH, Elsrafi M, El-Khoudary A, Elsaifi M, Aboul-Einein M, El-Bolkainy MN: Pediatric Hodgkin's disease in Egypt. Cancer 52:1129–1131, 1983.
38. Matawy MS, Omar YT: Hodgkin's disease in children in Kuwait. Cancer 57:2255–2259, 1986.
39. Pasqualini T, Iorcansky S, Gruñeiro L, Diez B, Pavlovsky S, Sackmann-Muriel F, Rivarola A: Thyroid Dysfunction in Hodgkin's Disease. Cancer 63:335–339, 1989.